

# Profile of incident chronic kidney disease related-mineral bone disorders in chronic kidney disease Stage 4 and 5: A hospital based cross-sectional survey

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## ABSTRACT

Chronic kidney disease related-mineral bone disorder (CKD-MBD) has been poorly studied in pre-dialysis Indian CKD patients. We aimed to study the clinical, biochemical and extra skeletal manifestations of untreated CKD-MBD in pre-dialysis Stage 4 and 5 CKD patients attending nephrology out-patient clinic at a tertiary care hospital in South India. A hospital based cross-sectional survey including, demographic profile, history of CKD-MBD symptoms, measurement of serum calcium, phosphate, parathyroid hormone, 25 hydroxy vitamin D (25(OH) D) and alkaline phosphatase; lateral abdominal X-rays for abdominal aortic calcification (AAC) and echocardiography for valvular calcification (VC) was carried out. Of the 710 patients surveyed, 45% had no CKD-MBD related symptom. Prevalence of hypocalcemia, hyperphosphatemia, hyperparathyroidism (>150 pg/mL) and 25(OH) D levels <30 ng/mL was 66.3%, 59%, 89.3% and 74.7% respectively. Echocardiography was carried out in 471 patients; 96% of whom had VC (calcification score ≥1). Patients with VC were older and had lower 25(OH) D levels than those without. Lateral abdominal X-rays were obtained in 558 patients, 6.8% of whom were found to have AAC, which was associated with older age. Indian patients with incident CKD-MBD have a high prevalence of hypocalcemia, 25(OH) D deficiency and VC even prior to initiating dialysis while AAC does not appear to be common. The association between 25(OH) D deficiency and VC needs further exploration.

**Key words:** Aortic calcification, chronic kidney disease related mineral bone disorder, pre-dialysis chronic kidney disease, valvular calcification, vitamin D

## Introduction

Chronic kidney disease (CKD) is now a public health problem affecting an estimated 10-13% of the world population.<sup>[1,2]</sup> As renal function declines, there is a progressive impairment in the regulation of mineral homeostasis leading to altered serum concentrations of calcium, phosphate, parathyroid hormone (PTH) and vitamin D. The end result of these biochemical

abnormalities is disordered bone growth and remodeling and extraskeletal calcification; collectively known as chronic kidney disease related-mineral bone disorders (CKD-MBD).<sup>[3]</sup>

CKD-MBD is receiving widespread attention due its association with cardiovascular mortality.<sup>[4]</sup> Early detection and treatment of CKD-MBD is an important aspect of CKD management; however, CKD-MBD in the Indian population has been poorly studied. We therefore, sought to study the clinical and biochemical features as well as radiological manifestations of vascular calcification in untreated CKD-MBD among pre-dialysis CKD Stage 4 and 5 patients attending nephrology out-patient clinic at our tertiary health-care facility, catering to patients from a large part of the Indian subcontinent.

## Subjects and Methods

### Patients

This cross-sectional survey was conducted at the Department of Nephrology, Christian Medical College

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Hospital, Vellore, Tamil Nadu, India. Consecutive incident Stage 4 and 5 CKD patients attending nephrology out-patient clinic between November 2009 and August 2010 who satisfied both the following criteria were included:

1. Patients with newly diagnosed Stage 4 and 5 CKD (based on history, estimated glomerular filtration rate [eGFR] of  $<30$  mL/min/1.73 m<sup>2</sup> by the abbreviated modification of diet in renal disease formula, biochemical and ultrasonographic/histological evidence of CKD) who were not yet on dialysis or on hemodialysis/CAPD for  $<1$  month at the time of enrolment in the study
2. Patients who had received calcium supplements/vitamin D analogs/phosphate binders for  $<3$  months and had no prior history of calcimimetic use.

We excluded patients who had received steroids/cyclosporine/anticonvulsants for  $>3$  months as well as patients on bisphosphonates. The study was approved by the Institutional Review Board and Ethics Committee of Christian Medical College, Vellore.

Figure 1 outlines the flow chart followed for patient selection. Each patient fulfilling criteria for inclusion in the study was interviewed to obtain information pertaining to demographic characteristics, socio-economic status

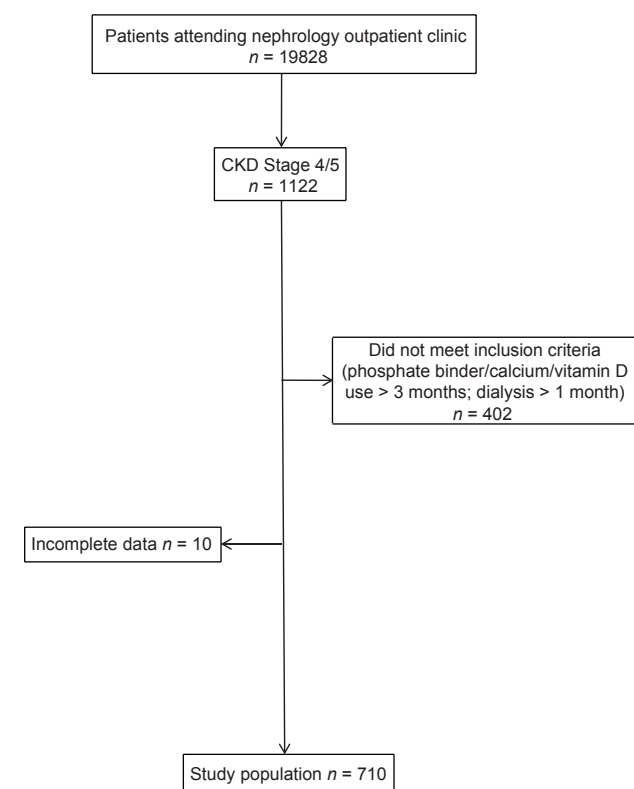


Figure 1: Protocol followed for patient selection

(modified Kuppasamy Scale), CKD-MBD symptoms (bone pain, proximal muscle weakness, fragility fractures, pruritus and red eyes), approximate daily sunlight exposure, medication, dialysis and dietary history. Proximal muscle weakness was defined as difficulty in getting up from a squatting position in the absence of hypokalemia, hypophosphatemia and steroid use for  $>3$  months. Fragility fractures were defined as fractures secondary to trivial trauma. Written informed consent was obtained in the appropriate format.

### Biochemistry

A fasting blood sample was drawn for measurement of biochemical parameters. PTH was measured in a simultaneously drawn plasma sample transported on ice to the laboratory, processed immediately and analyzed using a solid phase 2 site (1-34,44-84) chemiluminescent enzyme labeled immunometric assay (Immulite™, Diagnostics Products Corporation, CA, USA) with an intra and inter assay coefficient of variation of 5.7% and 8.8% respectively. 25 hydroxy vitamin D (25(OH) D) was measured in a fasting serum sample using the Elecsys modular analytics E170 immunoassay system (Roche Diagnostics, GmbH, Mannheim, Germany) with an intra- and inter-assay coefficient of variation of 5.7% and 7.1% respectively.

Normal values of serum calcium (corrected for albumin) and phosphate were defined as 8.5-9.5 mg/dL and 2.5-4.5 mg/dL respectively. Vitamin D deficiency, insufficiency and sufficiency were defined as  $<20$  ng/mL, 20-30 ng/mL and  $>30$  ng/mL. PTH level  $>150$  pg/mL (2 times the upper limit of the assay) was labeled as hyperparathyroidism.

### X-ray abdomen (lateral view)

Lateral abdominal X-ray to detect abdominal aortic calcification (AAC) was obtained according to a standard protocol and calcific lesions graded by a single radiologist blinded to clinical details using the index described by Kauppila *et al.*<sup>[5]</sup>

### Echocardiography

Echocardiography was carried out specifically for the purpose of this study, with patient in the left lateral decubitus position, using the parasternal long and short axis views, by a single cardiologist blinded to all clinical details. Calcification was defined as the presence of echo brightness exceeding that of normal valve tissue. A global calcification score was obtained by semi-quantitative assessment of valvular calcification (VC) at the following 8 sites as described by Pressman *et al.*<sup>[6]</sup>

1. Posterior annulus, by thirds (score 0-3)
2. Posterior mitral leaflet restriction (0 = absent, 1 = present)

3. Anterior annulus calcification (0 = absent, 1 = present)
4. Anterior mitral leaflet restriction (0 = absent, 1 = present)
5. Mitral valve (MV) calcification (0 = absent, 1 = mild, 2 ≥ mild)
6. Sub-valvular apparatus calcification (0 = absent, 1 = present)
7. Aortic valve (AV) calcification (0 = absent, 1 = nodule in <3 leaflets, 2 = nodules in 3 leaflets, non-restrictive; 3 = restrictive)
8. Aortic root calcification (0 = absent, 1 = present).

VC was defined as a calcification score  $\geq 1$  and significant VC was defined as a calcification score  $\geq 5$ .

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 16 (SPSS, Chicago, IL) as follows: Mean  $\pm$  S.D were used for normally distributed data and median and interquartile range for skewed data. Significance was determined by Two Independent sample *t* test for continuous data, Chi-square test for categorical data and Mann-Whitney *U* Test for skewed data. PTH and 25(OH) D, which had skewed distributions, were log transformed and Pearson's coefficients (for continuous variables with normal distribution) and Spearman's rank correlation coefficients (for categorical and non-normally distributed variables) were used to define their correlation with various clinical and biochemical parameters. Univariate analysis was performed using simple linear regression at 25% level of significance and the variables obtained were incorporated in the adjusted analysis using stepwise multiple linear regressions to arrive at the final models. The  $\beta$  coefficients obtained were expressed as the percentage change in the dependent variable for a unit change in the independent variable using the transformation  $(e^{\beta}-1) \times 100$ . To determine the clinical and demographic variables associated with VC and AAC, univariate analysis using binary logistic regression at 25% level of significance was carried out and variables which were significant were used to construct models using stepwise multivariate binary logistic regression. A  $P < 0.05$  was considered to be statistically significant for the adjusted analysis.

## Results

### Demographic profile

The study population of 710 patients comprised adults predominantly belonging to the lower and middle socio-economic strata with a mean age of  $46.6 \pm 13.4$  years, of whom 36.8% were diabetic, 81%

were hypertensive and males outnumbered females 2.7:1. No exposure to dialysis was present in 92%. Diabetic nephropathy was the most common native kidney disease, followed by chronic glomerulonephritis; however in 58.2% the native kidney disease was unknown due to late referral. Only 31.7% and 20.6% had received calcium supplements/calcitriol and phosphate binders respectively, indicating a largely treatment naïve cohort. The median daily milk consumption and sunlight exposure, which are correlates for nutritional vitamin D, were 100 mL and 1 hour respectively. Patients with CKD Stage 5 were younger, less likely to be diabetic and more often labeled as having an unknown native kidney disease [Table 1].

### CKD-MBD related symptoms

Table 2 shows that the most commonly reported symptoms were bone pain (33.5%), proximal muscle weakness (26.2%) and pruritus (25.5%); however 45% were asymptomatic. Three patients had fragility fractures (fracture neck of femur 2, vertebral fracture 1). There was no difference between Stage 4 and 5 CKD patients in the prevalence of CKD-MBD related symptoms.

### Biochemical parameters

Biochemical parameters are summarized in Table 3. Patients with CKD Stage 5 had a lower serum calcium and higher serum phosphate and PTH levels. Alkaline phosphatase and 25(OH) D levels were not significantly different between CKD stages. Overall, 66.3% were hypocalcemic, 59% were hyperphosphatemic and 89.3% had 25(OH) D levels  $< 30$  ng/mL. PTH level  $\geq 150$  pg/mL was present in 57.3% in CKD Stage 4 and 89.5% in CKD Stage 5. Owing to skewed distribution, PTH and 25(OH) D were log transformed and multiple linear regression was used to determine their clinical and biochemical associations after adjusting for age, gender, diabetic status, socio-economic status, body mass index (BMI), sunlight exposure, eGFR, calcium, phosphate and 25(OH) D where appropriate. Table 4a and b show the clinical and biochemical variables affecting serum PTH and 25(OH) D. High PTH was associated with low eGFR, low serum calcium, low 25(OH) D levels and female gender. Low 25(OH) D levels were associated with female gender, diabetes, higher socio-economic status and higher BMI.

### Valvular calcification

Echocardiographic evaluation was carried out in 471 patients. VC (calcification score  $\geq 1$ ), was present in 96%, and 51% had significant VC (calcification score  $\geq 5$ ). The mitral valve and posterior mitral annulus were the most common sites for calcification [Figure 2]. Mitral and aortic VC was present in 61.7%, 23.9% had only mitral

**Table 1: Patient and clinical characteristics of the study population by CKD stage**

|   | All (n = 710)             | Stage 4 (n = 225)         | Stage 5 (n = 485)         | P value |
|---|---------------------------|---------------------------|---------------------------|---------|
| Age (years)                             | 46.6±13.4                 | 51.5±12.0                 | 44.3±13.3                 | <0.001  |
| Age distribution                        |                           |                           |                           |         |
| <30 years                               | 104 (14.6)                | 14 (6.2)                  | 90 (18.6)                 | <0.001  |
| 30-50 years                             | 293 (41.3)                | 75 (33.3)                 | 218 (44.9)                |         |
| >50 years                               | 313 (44.1)                | 136 (60.4)                | 177 (36.5)                |         |
| Male gender                             | 517 (72.8)                | 163 (72.4)                | 354 (73)                  | 0.879   |
| Diabetes                                | 261 (36.8)                | 117 (52)                  | 144 (29.7)                | <0.001  |
| Native kidney disease                   |                           |                           |                           |         |
| Unknown                                 | 413 (58.2)                | 98 (43.6)                 | 315 (64.9)                | <0.001  |
| DN                                      | 221 (31.1)                | 97 (43.1)                 | 124 (25.6)                | 0.437   |
| CGN                                     | 24 (3.4)                  | 9 (4)                     | 15 (3.1)                  |         |
| ADPKD                                   | 16 (2.3)                  | 7 (3.1)                   | 9 (1.9)                   |         |
| CIN                                     | 12 (1.7)                  | 7 (3.1)                   | 5 (1)                     |         |
| Obstructive uropathy                    | 11 (1.5)                  | 3 (1.3)                   | 8 (1.6)                   |         |
| Renal calculus disease                  | 7 (1)                     | 0 (0)                     | 7 (1.4)                   |         |
| Arterionephrosclerosis                  | 6 (0.8)                   | 4 (1.8)                   | 2 (0.4)                   |         |
| Hypertension                            | 575 (81)                  | 186 (82.7)                | 389 (80.2)                |         |
| BMI                                     | 22.4±3.9                  | 22.6±3.9                  | 22.2±3.9                  | 0.192   |
| Smoking                                 | 112 (15.8)                | 35 (15.6)                 | 77 (15.9)                 | 0.913   |
| SES by modified Kuppuswamy scale        |                           |                           |                           |         |
| Lower class                             | 197 (27.2)                | 60 (26.7)                 | 137 (28.2)                | 0.503   |
| Middle class                            | 477 (67.2)                | 153 (68)                  | 324 (66.8)                |         |
| Upper class                             | 36 (5.1)                  | 12 (5.3)                  | 24 (4.9)                  |         |
| Vegan <sup>§</sup>                      | 134 (18.8)                | 47 (20.9)                 | 87 (17.9)                 | 0.350   |
| Milk intake in mL/day                   | 100 (0, 200) <sup>#</sup> | 100 (0, 250) <sup>#</sup> | 100 (0, 200) <sup>#</sup> |         |
| <250 mL/day                             | 629 (88.6)                | 189 (84)                  | 440 (90.7)                | 0.165   |
| 250-500 mL/day                          | 58 (8.2)                  | 26 (11.6)                 | 32 (6.6)                  |         |
| >500 mL/day                             | 23 (3.2)                  | 10 (4.4)                  | 13 (2.7)                  |         |
| Sun exposure in hours/day <sup>§</sup>  | 1 (0.5, 2) <sup>#</sup>   | 1 (0.5, 2) <sup>#</sup>   | 1 (0.5, 2.5) <sup>#</sup> |         |
| <1 h                                    | 422 (59.4)                | 144 (64)                  | 278 (57.3)                | 0.131   |
| 1-6 h                                   | 76 (10.7)                 | 17 (7.6)                  | 59 (12.2)                 |         |
| >6 h                                    | 212 (29.9)                | 64 (28.4)                 | 148 (30.5)                |         |
| MBD related medication usage            |                           |                           |                           |         |
| Calcium supplement usage                | 225 (31.7)                | 44 (19.6)                 | 181 (37.3)                | <0.001  |
| Duration of calcium use (days)          | 0 (0, 15) <sup>#</sup>    | 0 (0,0) <sup>#</sup>      | 0 (0,15) <sup>#</sup>     | <0.001  |
| Calcitriol use                          | 225 (31.7)                | 36 (16)                   | 189 (39)                  | <0.001  |
| Duration of calcitriol use (days)       | 0 (0,15) <sup>#</sup>     | 0 (0,0) <sup>#</sup>      | 0 (0,15) <sup>#</sup>     | <0.001  |
| Phosphate binder use                    |                           |                           |                           |         |
| Calcium acetate                         | 105 (14.8)                | 20 (8.9)                  | 85 (17.5)                 | 0.001   |
| Lanthanum carbonate                     | 21 (3)                    | 6 (2.7)                   | 15 (3.1)                  |         |
| Sevelamer hydrochloride                 | 20 (2.8)                  | 4 (1.8)                   | 16 (3.3)                  |         |
| None                                    | 564 (79.4)                | 195 (86.7)                | 369 (76.1)                |         |
| Duration of phosphate binder use (days) | 0 (0, 0) <sup>#</sup>     | 0 (0, 0) <sup>#</sup>     | 0 (0, 0) <sup>#</sup>     | 0.002   |
| Prior dialysis                          |                           |                           |                           |         |
| Haemodialysis                           | 55 (7.7)                  | 0 (0)                     | 55 (11.3)                 | <0.001  |
| Peritoneal dialysis                     | 2 (0.3)                   | 0 (0)                     | 2 (0.4)                   |         |
| No dialysis                             | 653 (92)                  | 225 (100)                 | 428 (88.2)                |         |
| Duration of dialysis in days            | 7 (7, 14.7) <sup>#</sup>  | 0 (0, 0) <sup>#</sup>     | 7 (7, 14.7) <sup>#</sup>  |         |

SD: Standard deviation, CKD: Chronic kidney disease, DN: Diabetic nephropathy, CGN: Chronic glomerulonephritis, ADPKD: Autosomal dominant polycystic kidney disease, CIN: Chronic interstitial nephritis, BMI: Body mass index, SES: Socio-economic status, MBD: Mineral bone disease. Variables are presented as percentage or mean±SD, as appropriate. <sup>#</sup>Median (Q1, Q3), <sup>§</sup>Sun exposure-average hours/day exposed to sunlight as per patient interview, <sup>§</sup>Vegan-no meat, fish, egg or dairy product consumption. Figures in parentheses are percentages

VC, 2.7% had only aortic VC and only 11.5% had neither valve calcified. There was no difference in age, gender, diabetic status, calcium, phosphorus, PTH levels or eGFR between patients with isolated mitral and isolated

aortic VC. The median cardiac calcification score and prevalence of significant calcification did not significantly differ between CKD Stage 4 and 5 [Table 5]. Table 6 compares clinical and biochemical parameters between

patients with and without VC. On stepwise binary logistic regression, adjusting for age, gender, diabetic status, hypertensive status, smoking, eGFR, calcium, phosphate, PTH and 25(OH) D levels, patients with VC (calcification score  $\geq 1$ ) were found to be older (odds ratio [OR]: 1.04, 95% confidence interval [CI]: 1.01-1.08,  $P = 0.017$ ) and had lower 25(OH) D levels (OR: 0.951, 95% CI: 0.91-0.99,  $P = 0.025$ ) compared with patients without VC (calcification score = 0).

### Abdominal aortic calcification

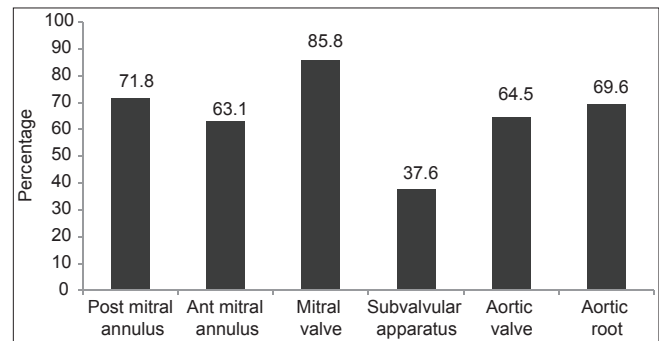
Lateral abdominal X-rays were available for 558 patients. AAC was seen in only 38 patients (6.8%), the most

common site being the posterior aortic wall opposite L3 and L4 vertebrae [Figure 3]. Table 7 shows that Stage 4 CKD patients had a higher prevalence of AAC (10% vs. 5.1%  $P = 0.03$ ) and significant AAC, defined as an anteroposterior segment score  $\geq 7$  (2.6% vs. 0.8%,  $P = 0.030$ ). Table 8 compares clinical characteristics between patients with and without AAC. Patients with AAC were older, predominantly male, diabetic, hypertensive and smokers. They also had a higher eGFR and consequently a lower phosphorus level compared with those without AAC. Using multivariate binary logistic regression, after adjustment for age, gender,

**Table 2: CKD MBD related symptoms**

| Symptom                  | Overall prevalence | Prevalence by CKD stage |                 | P value |
|--------------------------|--------------------|-------------------------|-----------------|---------|
|                          |                    | Stage 4 (n = 225)       | Stage 5 (n=485) |         |
| Bone pains               | 238 (33.5)         | 71 (31.6)               | 167 (34.4)      | 0.450   |
| Pathological fracture    | 3 (0.4)            | 1 (0.4)                 | 2 (0.4)         | 1.000   |
| Pruritus                 | 181 (25.5)         | 53 (23.6)               | 128 (26.4)      | 0.420   |
| Red eyes                 | 0 (0)              | 0 (0)                   | 0 (0)           | -       |
| Proximal muscle weakness | 186 (26.2)         | 48 (21.3)               | 138 (28.5)      | 0.045   |

CKD: Chronic kidney disease, MBD: Mineral bone disorders. Figures in parentheses are percentages

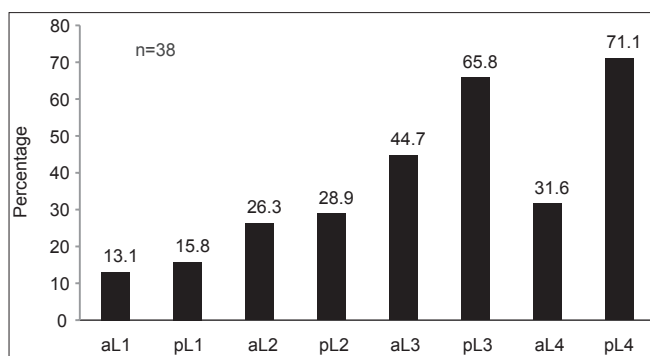


**Figure 2: Distribution of cardiac calcification. The percentage of patients with cardiac calcification at various sites as assessed by transthoracic echocardiography**

**Table 3: Laboratory parameters**

| Parameter                          | All (n = 710)     | Stage 4 (n = 225)    | Stage 5 (n = 485) | P value |
|------------------------------------|-------------------|----------------------|-------------------|---------|
| Hb (g/dL)                          | 8.8±1.9           | 9.8±1.9              | 8.4±1.7           | <0.001  |
| Urea (mg/dL)                       | 120 (85.7, 167)   | 71 (59, 92)          | 142 (109, 186.2)  | <0.001  |
| Creatinine (mg/dL)                 | 5.8 (3.6, 9.2)    | 3.0 (2.6, 3.7)       | 7.2 (5.5, 10.2)   | <0.001  |
| Bicarbonate (mmol/L)               | 18.2±4.7          | 20.8±4.1             | 17.0±4.5          | <0.001  |
| Albumin (g/dL)                     | 3.8±0.5           | 3.8±0.6              | 3.8±0.5           | 0.750   |
| cCa (mg/dL)                        | 8.0±1.0           | 8.4±0.6              | 7.8±1.1           | <0.001  |
| <8.5 mg/dL                         | 464 (66.3)        | 123 (55.7)           | 341 (71.2)        |         |
| 8.5-9.5 mg/dL                      | 221 (31.6)        | 92 (41.6)            | 129 (26.9)        |         |
| >9.5 mg/dL                         | 15 (2.1)          | 6 (2.7)              | 9 (1.9)           |         |
| Phosphate (mg/dL)                  | 5.3±1.9           | 3.8±0.77             | 5.9±2.0           | <0.001  |
| <2.5 mg/dL                         | 4 (0.6)           | 4 (1.8)              | 0 (0)             |         |
| 2.5-4.5 mg/dL                      | 287 (40.4)        | 173 (76.9)           | 114 (23.5)        |         |
| >4.5 mg/dL                         | 419 (59)          | 48 (21.3)            | 371 (76.5)        |         |
| PTH (pg/mL)                        | 285 (155, 527)    | 157.5 (101.1, 281.5) | 376 (228, 631)    | <0.001  |
| <150 pg/mL                         | 147 (20.7)        | 96 (42.7)            | 51 (10.5)         |         |
| 150-300 pg/mL                      | 177 (34.9)        | 66 (29.3)            | 111 (22.9)        |         |
| >300 pg/mL                         | 386 (54.4)        | 63 (28)              | 323 (66.6)        |         |
| 25 (OH) D (ng/mL)                  | 20.9±8.7          | 21.09±9.8            | 20.9±8.2          | 0.845   |
| <20 ng/mL                          | 307 (43.2)        | 114 (50.7)           | 193 (39.8)        |         |
| 20-30 ng/mL                        | 224 (31.5)        | 59 (26.2)            | 165 (34)          |         |
| >30 ng/mL                          | 179 (25.2)        | 52 (23.1)            | 127 (26.2)        |         |
| ALP (U/L)                          | 93 (73, 126)      | 93 (72.7, 126)       | 94 (73, 128)      | 0.543   |
| S. Chol (mg/dL)                    | 149 (121.7, 183)  | 155 (129.5, 181.2)   | 146 (117, 185)    | 0.052   |
| S. TG (mg/dL)                      | 116 (81.5, 164.5) | 133 (93.2, 180)      | 109.5 (78, 158)   | 0.003   |
| S. HDL (mg/dL)                     | 36 (29, 45)       | 35 (30, 45)          | 36 (29, 45)       | 0.482   |
| S. LDL (mg/dL)                     | 82 (63, 110)      | 87 (68, 113)         | 79 (61, 109.7)    | 0.056   |
| 24 h urine protein (g/day)         | 2.2 (0.8, 4.1)    | 1.7 (0.5, 4.7)       | 2.3 (1.1, 4)      | 0.184   |
| eGFR (mL/min/1.73 m <sup>2</sup> ) | 10.4 (16.3, 17.3) | 21.1 (17.7, 25.5)    | 8 (5.7, 11.0)     | <0.001  |

SD: Standard deviation, PTH: Parathyroid hormone, ALP: Alkaline phosphatase, Hb: Hemoglobin; cCa: Corrected calcium, PTH: Parathyroid hormone, 25(OH)D: 25 hydroxy vitamin D, ALP: Alkaline phosphatase, S. Chol: Serum cholesterol, S. TG: Serum triglycerides, S. HDL: Serum high density lipoprotein, S. LDL: Serum low density lipoprotein, eGFR: Estimated glomerular filtration rate by abbreviated modification of diet in renal disease equation. Variables are presented as mean±SD. Blood urea, serum creatinine, PTH, ALP, lipid profile, 24 h urine protein and eGFR are presented as median (Q1, Q3) because of skewed distribution. . Figures in parentheses are percentages or interquartile ranges.



**Figure 3: Distribution of abdominal aortic calcification.** The major sites of calcification among the 38 patients detected to have abdominal aortic calcification on X ray. On X axis, aortic segments are denoted as 'a' or 'p' referring to anterior or posterior aortic wall, followed by the lumbar vertebra opposite the aortic wall segment. (eg. aL1 refers to the anterior aortic wall opposite the first lumbar vertebra)

diabetic status, hypertensive status, eGFR and smoking, age was the only factor found to be independently associated with AAC (OR: 1.10, 95% CI: 1.05-1.15,  $P < 0.001$ ). There was no association between the presence of AAC and VC.

### Discussion

The prevalence of CKD in India has been estimated to range between 0.78% and 0.87%.<sup>[7,8]</sup> Despite the efforts of the CKD Registry of India, which collates data from an estimated 199 affiliated centers,<sup>[9]</sup> data regarding the characteristics of untreated CKD-MBD in pre-dialysis patients in India is scarce; a gap that this study specifically sought to bridge.

**Table 4a: Factors affecting serum PTH\***

| Independent variables | Unadjusted |           |         | Adjusted  |   |           |         |
|-----------------------|------------|-----------|---------|-----------|---|-----------|---------|
|                       | $\beta^s$  | 95% CI    | P value | $\beta^s$ | % change in PTH per unit change in variable | 95% CI    | P value |
| Age                   | 0.99       | 0.99-1.01 | 0.122   | -         | -   | -         | -       |
| Gender <sup>#</sup>   | 1.16       | 1.01-1.34 | 0.029   | 1.19      | 19  | 1.03-1.36 | 0.013   |
| eGFR                  | 0.96       | 0.95-0.97 | 0.001   | 0.96      | -3.8  | 0.95-0.97 | 0.001   |
| Diabetes <sup>#</sup> | 1.02       | 0.88-1.18 | 0.721   | -         | -   | -         | -       |
| Calcium               | 0.66       | 0.62-0.70 | 0.001   | 0.66      | -33.3                                       | 0.62-0.71 | 0.001   |
| Phosphate             | 0.98       | 0.93-1.02 | 0.436   | -         | -   | -         | -       |
| 25(OH)D               | 0.98       | 0.98-0.99 | 0.002   | 0.98      | -1.1  | 0.98-0.99 | 0.002   |

$R^2=0.388$ , PTH: Parathyroid hormone, 25(OH)D: 25 hydroxy vitamin D, eGFR: Estimated glomerular filtration rate by abbreviated modification of diet in renal disease equation, CI: Confidence interval. \*Log transformed due to skewed distribution, <sup>#</sup>Gender and diabetes were coded as continuous variables. Gender (0=male, 1=female), diabetes (0=no, 1=yes), <sup>s</sup> $\beta$  coefficients back-transformed to  $e^{\beta}$  (Odds ratio)

**Table 4b: Factors affecting serum 25(OH)D\***

| Independent variables | Unadjusted |           |         | Adjusted  |   |           |         |
|-----------------------|------------|-----------|---------|-----------|---|-----------|---------|
|                       | $\beta^s$  | 95% CI    | P value | $\beta^s$ | % change in 25(OH)D per unit change in variable | 95% CI    | P value |
| Age                   | 1.01       | 0.99-1.01 | 0.535   | -         | -   | -         | -       |
| Gender <sup>#</sup>   | 0.84       | 0.77-0.92 | 0.001   | 0.83      | -16.8   | 0.76-0.90 | 0.001   |
| eGFR                  | 0.99       | 0.99-1.01 | 0.540   | -         | -   | -         | -       |
| Diabetes <sup>#</sup> | 0.82       | 0.76-0.90 | 0.001   | 0.85      | -14.8   | 0.78-0.91 | 0.001   |
| SES <sup>#</sup>      | 0.87       | 0.81-0.93 | 0.001   | 0.86      | -13.8   | 0.80-0.92 | 0.001   |
| BMI                   | 0.98       | 0.97-0.99 | 0.001   | 0.98      | -1.5  | 0.97-0.99 | 0.002   |
| Sun exposure          | 1.01       | 0.99-1.01 | 0.169   | -         | -   | -         | -       |

$R^2=0.111$ , 25(OH)D: 25 hydroxy vitamin D, eGFR: Estimated glomerular filtration rate by abbreviated modification of diet in renal disease equation, SES: Socio-economic status by modified Kuppuswamy scale, BMI: Body mass index, CI: Confidence interval. \*Log transformed due to skewed distribution, <sup>#</sup>Gender, diabetes and SES were coded as continuous variables. Gender (0=male, 1=female), SES (0=lower class, 1=middle class, 2=upper class), diabetes (0=no, 1=yes), <sup>s</sup> $\beta$  coefficients back-transformed to  $e^{\beta}$  (Odds ratio)

**Table 5: Echocardiographic calcification scores across CKD Stage 4 and 5**

| Calcification indices  | Overall (n = 471) | CKD Stage 4 (n = 161) | CKD Stage 5 (n = 310) | P value |
|--|-------------------|-----------------------|-----------------------|---------|
| Calcification at $\geq 1$ site (n, %)                                | 452 (96)          | 153 (95)              | 299 (96.5)            | 0.457   |
| Calcification score  |                   |                       |                       |         |
| Median (Q1, Q3)  | 5 (3, 6)          | 4 (3, 6)              | 5 (3, 6)              | 0.057   |
| Range  | 0-12              | 0-10                  | 0-12                  |         |
| Presence of significant cardiac calcification: Score $\geq 5$ (n, %) | 240 (51)          | 76 (47.2)             | 164 (52.9)            | 0.24    |

Q1: First quartile, Q3: Third quartile, CKD: Chronic kidney disease

**Table 6: Clinical and biochemical characteristics of patients with and without VC**

| Characteristics                       | Cardiac calcification |                    | P value |
|---------------------------------------|-----------------------|--------------------|---------|
|                                       | Absent (n = 19)       | Present (n = 452)  |         |
| Age (years)                           | 39.18±11.55           | 47.15±13.03        | 0.014*  |
| Male gender (%)                       | 15 (78.9)             | 320 (70.8)         | 0.442   |
| eGFR (mL/min/1.73 m <sup>2</sup> )    | 9.85 (5.53, 17.94)    | 11.10 (7.05, 17.7) | 0.885   |
| BMI (kg/m <sup>2</sup> )              | 22.20±4.52            | 22.37±3.90         | 0.852   |
| Smoking (%)                           | 1 (5.3)               | 74 (16.4)          | 0.334   |
| Diabetes (%)                          | 6 (31.6)              | 174 (38.5)         | 0.543   |
| Years since diagnosis of diabetes     | 0 (0, 5)              | 0 (0, 7)           | 0.347   |
| Hypertension (%)                      | 18 (94.7)             | 376 (83.2)         | 0.182   |
| Years since diagnosis of hypertension | 1 (0.1, 4)            | 2 (0.25, 5)        | 0.300   |
| S. Chol (mg/dL)                       | 138 (117.5, 188)      | 150 (122.5, 184)   | 0.230   |
| S. TG (mg/dL)                         | 117 (68.5, 174)       | 117.5 (82, 163)    | 0.920   |
| S. HDL (mg/dL)                        | 34 (27, 42.2)         | 37 (30, 46)        | 0.269   |
| S. LDL (mg/dL)                        | 72 (45, 107.7)        | 84 (63, 110)       | 0.104   |
| cCa (mg/dL)                           | 7.96±0.88             | 8.03±1.03          | 0.768   |
| Phosphate (mg/dL)                     | 5.84±2.37             | 5.18±1.93          | 0.150   |
| PTH (pg/mL)                           | 356.5 (126.7, 775.25) | 301 (167, 512)     | 0.453   |
| 25(OH)D (ng/mL)                       | 25.34±11.99           | 20.82±8.81         | 0.032*  |

SD: Standard deviation, VC: Valvular calcification, eGFR: Estimated glomerular filtration rate by abbreviated modification of diet in renal disease equation, BMI: Body mass index, S. Chol: Serum cholesterol, S. TG: Serum triglycerides, S. HDL: Serum high density lipoprotein, S. LDL: Serum low density lipoprotein, cCa: Corrected calcium, PTH: Parathyroid hormone, 25(OH)D: 25 hydroxy vitamin D. Variables are presented as percentage or mean±SD, as appropriate. eGFR, diabetes and hypertension duration, lipid profile, PTH are expressed as median (Q1, Q3) due to skewed distribution. \*Significant (P<0.05) on univariate and multivariate analysis

**Table 7: Abdominal aortic calcification scores by CKD stage using the Kauppila index**

| Aortic calcification indices          | Overall (n = 558) | Stage 4 (n = 189) | Stage 5 (n = 369) | P value |
|---------------------------------------|-------------------|-------------------|-------------------|---------|
| AAC prevalence (n, %)                 | 38 (6.8)          | 19 (10.1)         | 19 (5.1)          | 0.030*  |
| Affected segment score (0-4)          |                   |                   |                   |         |
| Mean±SD                               | 2.1±1             | 2.2±1.1           | 2.1±1             | 0.881   |
| Median score                          | 2                 | 2                 | 2                 |         |
| Range                                 | 1-4               | 1-4               | 1-4               |         |
| Anteroposterior affected score (0-8)  |                   |                   |                   |         |
| Mean±SD                               | 2.9±1.7           | 3.1±2             | 2.7±1.4           | 0.527   |
| Median score                          | 3                 | 3                 | 3                 |         |
| Range                                 | 1-7               | 1-7               | 1-6               |         |
| Anteroposterior severity score (0-24) |                   |                   |                   |         |
| Mean±SD                               | 4.1±2.8           | 4.6±3.3           | 3.6±2.2           | 0.284   |
| Median score                          | 3                 | 3                 | 3                 |         |
| Range                                 | 1-11              | 1-11              | 1-8               |         |
| Significant AAC (APSS≥7) (%)          | 8 (1.4)           | 5 (2.6)           | 3 (0.8)           | 0.030*  |

CKD: Chronic kidney disease, AAC: Abdominal aortic calcification, APSS: Anteroposterior severity score, SD: Standard deviation. \*Significant (P<0.05)

The study population comprised predominantly young and middle aged patients belonging to the low and middle income group, with males outnumbering females 3:1, which is representative of the referred CKD population in India.<sup>[9]</sup> In 45%, no CKD-MBD related symptom was found, reinforcing the fact that CKD-MBD is a clinically silent disease.

The high prevalence of 25(OH) D deficiency, hypocalcemia and hyperparathyroidism in this study is consistent with findings from previous hospital based surveys on CKD-MBD in India.<sup>[10,11]</sup> Although not considered an essential component of CKD-MBD assessment in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, 25(OH) D deficiency plays an important role

in modifying and potentiating CKD-MBD in the Indian subcontinent and its ubiquitous presence has a deep rooted nutritional, genetic and socio-economic basis. This includes, low dietary intake of vitamin D, lack of a national vitamin D food fortification program,<sup>[12]</sup> increased activity of the 25(OH) D degrading enzyme 25(OH) D 24 hydroxylase in skin fibroblasts of Indians<sup>[13]</sup> and dark skin pigmentation requiring longer exposure to ultraviolet (UV) rays to achieve adequate 25(OH) D levels.<sup>[14]</sup> Patients of a higher socio-economic status, in whom 25(OH) D deficiency is more common,<sup>[15]</sup> reside in cities, where atmospheric pollution, cramped living spaces and sedentary occupation reduce their exposure to UV rays, compared with laborers and farmers who comprise the lower socio-economic strata.<sup>[16]</sup> They are

**Table 8: Clinical and biochemical characteristics of patients with and without AAC**

| Characteristics                       | Abdominal aortic calcification |                     | P value  |
|---------------------------------------|--------------------------------|---------------------|----------|
|                                       | Absent (n = 520)               | Present (n = 38)    |          |
| Age (years)                           | 46.52±12.87                    | 56.63±8.13          | <0.001** |
| Male gender (%)                       | 366 (70.4)                     | 32 (84.2)           | 0.029*   |
| eGFR (mL/min/1.73 m <sup>2</sup> )    | 11.24 (6.84, 17.44)            | 14.84 (9.61, 22.12) | 0.004*   |
| BMI (kg/m <sup>2</sup> )              | 22.33±3.91                     | 22.85±3.39          | 0.444    |
| Smoking (%)                           | 80 (15.4)                      | 11 (28.9)           | 0.029*   |
| Diabetes (%)                          | 188 (36.2)                     | 25 (65.8)           | <0.001*  |
| Years since diagnosis of diabetes     | 0 (0, 5)                       | 9.5 (0, 15)         | <0.001*  |
| Hypertension (%)                      | 420 (80.8)                     | 36 (94.7)           | 0.032*   |
| Years since diagnosis of hypertension | 1 (0.25, 5)                    | 5 (1.87, 10.5)      | <0.001*  |
| S. Chol (mg/dL)                       | 149 (121, 184)                 | 163 (135, 180)      | 0.875    |
| S. TG (mg/dL)                         | 115 (81, 165)                  | 119 (83, 141)       | 0.327    |
| S. HDL (mg/dL)                        | 36 (30, 45)                    | 38 (32, 47)         | 0.114    |
| S. LDL (mg/dL)                        | 81 (62, 110)                   | 91 (72, 113)        | 0.978    |
| cCa (mg/dL)                           | 8.02±1.03                      | 8.36±0.68           | 0.049    |
| Phosphate (mg/dL)                     | 5.18±1.83                      | 4.36±1.20           | 0.007*   |
| PTH (pg/mL)                           | 285 (152.75, 512.25)           | 250 (154, 396.75)   | 0.106    |
| 25(OH)D (ng/mL)                       | 21.05±9.02                     | 19.40±6.76          | 0.275    |

SD: Standard deviation, AAC: Abdominal aortic, eGFR: Estimated glomerular filtration rate by abbreviated MDRD equation, BMI: Body mass index, S. Chol: Serum cholesterol, S. TG: Serum triglycerides, S. HDL: Serum High density lipoprotein, S. LDL: Serum Low density lipoprotein, cCa: Corrected calcium, PTH: Parathyroid hormone, 25(OH)D: 25 hydroxy vitamin D. Variables are presented as mean±SD for normally distributed continuous data, median (first, third quartile) for skewed data and n, % for categorical data.\*Significant (P<0.05) on univariate analysis \*\* Significant (P<0.05) on univariate and multivariate analysis

also more likely to be obese, leading to sequestration of cutaneously synthesized and dietary vitamin D in adipose tissue and low bioavailability.<sup>[17,18]</sup> Women in particular, have low 25(OH) D levels due to poor dietary intake, multiple unplanned, unspaced pregnancies and because 75% have less than 1 hour of sunlight exposure per day.<sup>[19]</sup> The higher prevalence of hyperparathyroidism in women is therefore a reflection of 25(OH) D deficiency. Diabetes, a national epidemic of sorts, is also associated with 25(OH) D deficiency as the latter has been shown to impair insulin secretion.<sup>[20]</sup>

VC on echocardiography was assessed using a global calcification scoring system described by Pressman *et al.*<sup>[6]</sup> The mitral valve and posterior mitral annulus were the most common sites of calcification in our study. While aortic VC increases with age and is considered a degenerative process, mitral annular calcification is more strongly associated with abnormalities in mineral metabolism.<sup>[21]</sup> However, this study did not demonstrate any difference in biochemical parameters between patients with isolated mitral or aortic VC.

Of the 471 patients assessed, 96% had calcification at one of eight valvular sites (i.e. calcification score of ≥1) and none had underlying rheumatic or intrinsic valvular disease. The prevalence of mitral VC (85.8%) and aortic VC (64.5%) in this study was much higher than that reported in Caucasian pre-dialysis CKD subjects (31% combined mitral and aortic VC) by Leskinen *et al.*<sup>[22]</sup> Ghosh *et al.*, reported VC in 25% and 46% of Indian

CKD Stage 4 and 5D patients respectively. In contrast, the prevalence of mitral and aortic VC in healthy Indian subjects aged 60-64 is only 2% and 28% respectively.<sup>[23]</sup> Thus, even prior to calcium and vitamin D analog supplementation, the prevalence of VC in young and middle aged CKD patients is significantly higher than that of healthy elderly Indian subjects, indicating that CKD itself promotes VC, as has been confirmed by studies in the West.<sup>[24]</sup> However, the higher prevalence of VC in Indian CKD patients compared with their Caucasian counterparts indicates that there may be geographic or genetic risk factors for VC unique to the Indian subcontinent, though this has not been studied either in the CKD or the general population. In this study, patients with VC were older and had lower 25(OH) D levels compared with those without VC. While the association of age with VC is in concordance with previously published data,<sup>[22,25]</sup> Vitamin D has a U shaped relation with vascular calcification, with both low and high levels associated with an increased risk of extraskeletal calcification.<sup>[26]</sup> Vitamin D deficiency has been postulated to promote calcification through inflammatory cytokine release, decrease in calcification inhibitors such as fetuin-A and matrix Gla protein, and inhibition of klotho, one of whose roles is to prevent extraskeletal osteoblastic matrix deposition.<sup>[27]</sup> While the association between 25(OH) D deficiency and VC in this study does not prove causation, the nature and significance of this association requires further clarification through prospective longitudinal studies in Indian CKD patients. Aortic and mitral VC have been



associated with a 1 year all-cause mortality of 57%, compared with 15% in patients with neither valve calcified,<sup>[28]</sup> and hence such widespread prevalence of VC even prior to dialysis initiation is a cause for concern.

AAC as assessed by lateral abdominal X-ray was found in 6.8% of the 558 patients surveyed. Lateral abdominal X-ray calcification score of  $\geq 7$  has sensitivity and specificity of 67% and 91% for coronary artery calcification (CAC) score of  $\geq 100$  Agatston units on electron beam computed tomography (EBCT).<sup>[29]</sup> Thus, despite a lower sensitivity, the presence of significant AAC on X-ray is strongly associated with a significant CAC and according to KDIGO guidelines,<sup>[3]</sup> can be used as a screening tool in the absence of EBCT.

Our study had a very low prevalence of AAC compared with studies involving Caucasian CKD patients,<sup>[30-33]</sup> which have reported a 49-90% prevalence on multislice computed tomography (MSCT) in Stage 3 and 5 CKD patients with a mean age of 58-71 years. Shantha *et al.*, using a lateral abdominal X-ray for screening, found a prevalence of 76.9% in 26 Indian pre-dialysis Stage 5 CKD patients who had a mean age of 56.6, 65% of whom were receiving calcium containing phosphate binders.<sup>[34]</sup> We found AAC to be associated with traditional risk factors for atherosclerosis such as age, diabetes, hypertension, smoking and male sex, though only the association with age was found to be significant on adjusted analysis. Thus, AAC in pre-dialysis patients appears to be the result of calcification of atherosclerotic plaque as described in the general population. The low prevalence of AAC in this study is due to both the lower sensitivity of the screening modality and a younger study population (mean age 46.6 years) who had not received long-term calcium or vitamin D supplements.

The higher prevalence and greater severity of AAC in Stage 4 CKD patients is explained by the fact that Stage 4 CKD patients were older. Data from the CKD registry of India, also suggests that Stage 5 CKD patients in India are younger than patients in Stage 3 and 4 CKD at presentation,<sup>[9]</sup> which is an indirect indicator of the mortality associated with CKD in the elderly.<sup>[35]</sup> Since aortic calcification has been linked to all cause and cardiovascular mortality in the general<sup>[36]</sup> and dialysis population,<sup>[37]</sup> the presence of AAC by Stage 4 CKD may identify a subgroup of patients at high-risk for cardiovascular events who may benefit from more aggressive management of modifiable atherosclerotic risk equivalents.

This study has several strengths. This is the largest study to specifically assess untreated CKD-MBD in pre-dialysis

Indian patients. The exclusion of patients who had received calcium supplements, phosphate binders or vitamin D analogs for >3 months allowed a more robust assessment of biochemical parameters at baseline. Ours is also the first study to use a semi-quantitative echocardiographic scoring system to assess global cardiac calcification burden in CKD patients. Although yet to be validated in CKD, the study from which this scoring system was derived<sup>[6]</sup> found a score of  $\geq 5$  to have a positive predictive value of 60% for a CAC score of  $\geq 400$  on MSCT and hence this scoring system can be used as a substitute for EBCT/MSCT in resource poor settings. Compared with most other CKD-MBD studies, which reported calcification at the mitral and/or aortic valve alone, the use of a calcification score assessing calcification at eight valvular sites increased the sensitivity for detection of VC and partly explains its high prevalence in the study subjects. Significant VC (score  $\geq 5$ ) was found in 51%, suggesting that in a majority, the calcification was likely to be of clinical significance.

The inherent limitation of a hospital based survey involving a referred patient population is that it cannot describe the epidemiology of CKD-MBD in the community. Although mean age, gender ratio, etiology of kidney disease, diabetic and socio-economic status of patients in this study is similar to the standard referred population described in the CKD registry of India,<sup>[9]</sup> population based surveys that have assessed the prevalence of CKD in India have shown the mean age of CKD patients to range from 52 to 59 years, 48-61% of whom are males.<sup>[7,38]</sup> Thus, a cross sectional survey of CKD-MBD in the community would have had an older patient cohort and a greater female representation than the present study. This in turn may have yielded a higher prevalence of 25(OH) D deficiency, hyperparathyroidism, VC and AAC than this study reported. Despite the potentiating effect of 25(OH) D deficiency on CKD-MBD as shown in this study, its measurement is not an essential component of CKD-MBD assessment as per the KDIGO guidelines.<sup>[3]</sup> In addition, 25(OH) D levels are influenced by a variety of environmental, socio-economic and genetic factors, already alluded to previously, which were not assessed in this study. Cardiac and aortic calcification could not be assessed in all subjects due to logistic reasons; however, baseline characteristics did not differ between those with and without these investigations. Bone histomorphometry for histological assessment of CKD-MBD and EBCT/MSCT to assess vascular calcification were not available at our center due to resource limitations. The lack of a sensitive imaging modality may partly explain the low prevalence of AAC in the study population. Lastly, although intriguing, the cross-sectional nature of the study design does not allow us to establish a direct causal

relationship between 25(OH) D deficiency and the high prevalence of VC.

To conclude, this survey reveals a huge burden of hypocalcemia, vitamin D deficiency and VC in Indian CKD patients, well-established by the pre-dialysis stage. VC is associated with older age and vitamin D deficiency. AAC is associated with older age and is uncommon. The association between vitamin D deficiency and VC needs to be further clarified through experimental and prospective longitudinal studies.

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